Automated High Throughput Liquid-Liquid Extraction Screen for Reaction Workups in Chemical Process Development

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Liquid-liquid extractions are commonly used across chemical process development to remove any undesired components including solvents, impurities, and catalysts from a reaction. Traditionally, these extractions are performed on a large scale and are therefore, low throughput, labour intensive, and time consuming. High-throughput techniques have been increasingly applied to accelerate chemical process development, executing many reactions across a wide design space and generating large data sets in a shorter period of time. This includes crystallisations and reaction optimisations, but less has been done regarding high-throughput reaction workup, as this workflow requires the implementation of state-of-the-art robotic platforms and the set-up of complex data management systems to collate information from different analytical techniques.

Herein, we outline the automated liquid-liquid extraction workflow that has been developed for immiscible organic and aqueous phases as part of the high throughput strategy in Chemical Development at GSK. The Unchained Labs Freeslate CM3 automated platform was used in this workflow for solid handling, pH measurements, vial weighing for density calculations and liquid handling (allowing for the automated sampling of the organic and aqueous phases of up to 6 vials at once to obtain accurate density values for each phase). The automated platform was also used to take images of the vials which were then run through a fit-for-purpose MATLAB^{TM} code, an automated image analysis script for determining phase volumes.

A 30-second high-throughput UPLC method was applied, along with KF and NMR to understand API recovery, partitioning of all reaction components and obtain a full mass balance. In partnership with Metrohm, an industry-first high-throughput KF instrument, capable of handling plates in a fully automated workflow, was developed.

Several process parameters such as mixing rate and time, concentrations and pH, were systematically investigated to maximise the yield/purity of the desired product.

This work also covers and critically analyses the challenges the workflow faced and the developments that have since been made to overcome these. The workflow demonstrates the importance of high-throughput technologies and their applicability in chemical process development in lieu of traditional manual methods, allowing this to be continually applied to projects in Chemical Development.